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EXAMINER	
QAZI, SABIHA NAIM	
ART UNIT	**PAPER NUMBER**
1616	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/641,327	Applicant(s) AGOSTON ET AL.	
	Examiner Sabiha N. Qazi	Art Unit 1616	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *18 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Final Office Action

Acknowledgment id made of the response filed on 11/18/03. Amendments are entered. Claims 10-30 are pending. No claim is allowed.

This application is drawn to method of treating angiogenesis by 2-substituted estradiols of claims 10-30.

Examiner noticed that the Applicants did not amend the claims according to the rules, which could have made the application allowable, but instead prolonged the prosecution of this application. Applicants should amend the claims to a small subgenus for which they have the support in the specification.

Arguments were fully considered but are not found persuasive therefore rejection is maintained.

Examiner disagrees with the arguments made by Applicants. In response to (3a) of Applicant's argument, the Applicant's Specification on page 20, lines 20-25 (Table 1) does not show methods for inhibiting angiogenesis by any of the compounds of Formula I. There is no mention of the inhibition of angiogenesis.

The Applicants argue, "Claims 12-18 are each drawn to a single 16-substituted 2-methoxystradiol compound..." Examiner agrees that the claims are drawn to a single 16-substituted 2-methoxystradiol compound, but disagrees with the predictability of inhibiting angiogenesis. There is only one example in the specification for a single 16-methyl-substituted 2-methoxystradiol compound; the claims are broad and the predictability in the pharmaceutical art, especially in the steroids, is very, very low. There should be a reasonable expectation that one skilled in the art would not have to go undue experimentation to make and use the presently

claimed invention. There is no enablement or written description in the disclosure. 16-substituted estradiol compounds are ***not*** the same as estradiol.

It is unclear to the Examiner what R is in Table 2 (Example 24, Page 33). Examiner could not find R in ***any*** of the structures throughout the specifications or the amended claims.

Applicants argue, "Applicants are not aware of any provision in the MPEP requiring Applicants to predict the activity of all the estradiol derivatives of Claims 10 and 19." Examiner does not want Applicants to predict the activity of all the estradiol derivatives. Examiner wants a reasonable expectation so that one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation.

According to Applicant's own specification, "All of the 2-modified analogs presented in Table 1 have significantly less estrogenic activity (compared to estradiol) as represented by their proliferation index in estrogen dependent MCF-7 cells." (Lines 23-25 on page 20) This means that a minor modification may bring a drastic change in the activity of these compounds. The basis of enablement by the Examiner is the same—the prediction of a wide and broad range of compounds for the use of such as inhibiting the angiogenesis is not probable.

Since the method of use as claimed involves a broad range of compounds of Claims 10 and 19, there is a lack of enablement and written description in the specification. Claims stand rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-30 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Following reasons apply.

1. In evaluating the enablement question, several factors are to be considered. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: Instant claims are drawn to the method of treating angiogenesis by 2-substituted estradiol derivatives of formula in claim 10 and 19.

2) The state of the prior art: Prior art of record teaches method of treatment of angiogenesis, for example 2-methoxy estradiol, 2-ethoxy estradiol, 2-alkoxyestradiol derivatives, esterone, 2-hydroxyalkylestradiols, 2-methoxyoesterone-3-O-sulfamate. All the compounds are estradiol or esterone derivative known to treat angiogenesis or cancer.

3) The predictability in the art: There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). The unpredictability of the steroid art is very high. *Applicants own disclosure can be taken as example for lack of predictability, on page 20 lines 20-25, it has been shown that 2-methylhydroxy and 2-formyl derivatives had good antiproliferative activity (IC50<10microM) in HUVEC cells whereas 2-acetyl derivative was found with poor activity in the same assay. The difference in range is less than 10 to 18, which is large. Furthermore, 2-methylhydroxy and 2-formyl derivatives were inactive in breast tumor MDA-MB-231 cells while 2-acetyl estradiol had good activity in this cell line.*

It should be clear from these results and discussion that to predict the activity of hundreds of compounds as instantly claimed seems to be impossible. See *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must

appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat* et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724. Therefore, predicting the activity of all the estradiol derivatives as in claims 10 and 19 is impossible.

4) The presence or absence of working examples:

On page 20, Table 1 shows the test data for the compounds 2-methylhydroxy-E2, 2-formyl-E2 and 2-acetyl-E2 (2ME2 is known), all these compounds are 2-substitued others are hydrogen. The methods which is presently claimed There is no data for compounds having variety of substituent at 1, 2, 3, 4, 6, 16 and 17 (other than C-OH) of the steroid as presently claimed, which would assist the skilled artisan in practicing the claimed invention.

5) The breadth of the claims: Claims are drawn to the method of treatment of angiogenesis by hundreds of compounds as in claims 10 and 19, therefore, claims are considered broad and includes method of inhibiting angiogenesis by variety of compounds as in claims 10-30

6) The quantity of experimentation needed: Since the nature of the method is so unpredictable, as can be seen by the prior art cited above and since the claims are drawn to a broad range of pharmaceuticals for treatment of angiogenesis and since there is a lack of guidance present in the specification, the skilled artisan would have to undertake undue experimentation to practice the claimed invention commensurate with the scope of the claims. The skilled artisan, seeking lead

compounds for pharmaceutical discovery and treatment of angiogenesis, would be at a loss as to where to begin such discovery in the absence of such data.

Since biological activity such as angiogenesis cannot be predicted and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine the activity of all the estradiol analogues as presently claimed have the property of angiogenesis.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha N. Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sabiha N. Qazi

Primary Examiner

Art Unit 1616

5/1/04